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Editorial

PDF OF THIS ARTICLE

See Related:
Articles
Authors' Articles

Return to Table of Contents

INTRODUCTION

AUTHOR/ARTICLE INFORMATION

REFERENCES

Failure of Estrogen Plus Progestin Therapy for Prevention

Suzanne W. Fletcher, MD, MSc; Graham A. Colditz, MD, DrPH

Approximately 38% of postmenopausal women in the United States use hormone replacement therapy.[1] In 2000, 46 million prescriptions were written for Premarin (conjugated estrogens), making it the second most frequently prescribed medication in the United States and accounting for more than $1 billion in sales, and 22.3 million prescriptions were written for Prempro (conjugated estrogens plus medroxyprogesterone acetate).[2] While US Food and Drug Administration–approved indications for hormone therapy include relief of menopausal symptoms and prevention of osteoporosis, long-term use has been in vogue to prevent a range of chronic conditions, especially heart disease. Estrogen alone was the dominant hormone until the increased risk of endometrial cancer led to the addition of progestins for women with an intact uterus. Since the mid-1980s, combined estrogen/progestin use has steadily increased.[3]

Evidence on the potential risks and benefits of combined estrogen/progestin has slowly accumulated, suggesting that the combination acts differently than estrogen alone. Several studies found a link between duration of estrogen/progestin use and breast cancer risk.[4-8] Addition of progestins may increase risk above that observed with estrogen alone, as mitotic activity in the breast during normal menstrual cycles is greatest when progesterone levels are highest.[9]

Early evidence from studies of unopposed estrogen suggested it lowered risk of cardiovascular disease, consistent with results from studies of intermediate markers that showed beneficial changes.[10] However, recent evidence from secondary prevention trials and observational studies using combined estrogen/progestin therapy showed increased risk of coronary heart disease in the first year.[11-13] This may reflect prothrombotic and proinflammatory effects of progestins that outweigh any effects of estrogens on atherogenesis and vasodilatation.

Now, the surprising results of the Women's Health Initiative (WHI) are reported in this issue of THE JOURNAL.[14] The WHI is the first randomized primary prevention trial of postmenopausal hormones, and the part of the study that compared estrogen/progestin with placebo was terminated early. The data and safety monitoring board (DSMB) recommended stopping the trial because women receiving the active drug had an increased risk of invasive breast cancer (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.00-1.59),

INTRODUCTION

AUTHOR/ARTICLE INFORMATION

REFERENCES

and an overall measure suggested that the treatment was causing more harm than good (global index, 1.15; 95% CI, 1.03-1.28). The decision to stop the trial after an average follow-up of 5.2 years (planned duration, 8.5 years) was made when these results met predetermined levels of harm. However, several other outcomes also suggested harm, including increased coronary heart disease (HR, 1.29; 95% CI, 1.02-1.63), stroke (HR, 1.41; 95% CI, 1.07-1.85), and pulmonary embolism (HR, 2.13; 95% CI, 1.39-3.25). Beneficial results included decreases in colorectal cancer (HR, 0.63, 95% CI, 0.43-0.92) and hip fracture (HR, 0.66; 95% CI, 0.45-0.98). Numbers of overall deaths in the estrogen/progestin and placebo groups were statistically and clinically similar in this short-duration study. Most adverse outcomes began appearing within 1 to 2 years, but increased breast cancer risk did not begin until 3 years. Results were remarkably consistent in subgroup analyses, suggesting that there is not a subgroup that the drug benefits.

The DSMB did not recommend stopping the other portion of the hormone replacement trial, which compared estrogen alone with placebo in women with hysterectomies, so it is reasonable to assume that to date, estrogen alone may be safer than combination estrogen/progestin.

The methods of the WHI study appear strong. A total of 16 608 women entered the randomized double-blind trial, and the active treatment group and the placebo group appeared to be comparable at baseline. It is interesting that such a large number of women were willing to participate in a study of a commonly used and accepted drug, and perhaps equally remarkable that only 3.5% were lost to follow-up. Clinicians were unblinded for 40.5% of women in the active treatment group and 6.8% of the placebo group, usually because of persistent vaginal bleeding. The types of outcomes and standardized procedures for measurements make it unlikely that this degree of unblinding affected results. During the study, 42% of women receiving active drug and 38% of those receiving placebo stopped taking their assigned medications, and 6.2% and 10.7%, respectively, initiated hormone therapy. Therefore, as the authors suggest, the reported findings of the intention-to-treat analysis may have underestimated the true effects. Also, if duration of treatment is important, as appears to be the case with breast cancer risk, and if compliance decreases over time, 5-year results may underestimate longer-term treatment effects. The investigators took into account competing risks of therapy and created a global index of major medical events to give an overall assessment of benefits and harms.

INTRODUCTION

AUTHOR/ARTICLE INFORMATION

REFERENCES

The authors present both nominal and rarely used adjusted CIs to take into account multiple testing, thus widening the CIs. Whether such adjustments should be used has been questioned,[15] but nominal CIs are appropriate for breast cancer, coronary heart disease, and the global index outcomes because they were the preselected major outcomes of the trial. Also, the consistency of the results over the 5 years of the study, as shown in Table 4 of the article and in the figures, argues against spurious statistical results.

Overall, the results of the WHI study are consistent with the growing body of literature on the effects of combination estrogen/progestin. The increasing risk of breast cancer with duration of use and the reductions in risk of colon cancer and fractures are in the expected

direction and magnitude. Risk for stroke and venous thromboembolism continued throughout the 5 years of therapy, whereas the elevated risk of coronary heart disease was largely limited to the first year of therapy, as occurred in the Coumadin Aspirin Reinfarction Study[12] and the Heart and Estrogen/progestin Replacement Study.[11, 16]

How should practicing clinicians and the millions of women taking an estrogen/progestin combination react to the unexpected and disquieting results of this study? First, although the trial results are reported primarily in terms of relative risk, which is appropriate for studies of cause, when applying the results to practice, they must be translated into absolute risk. The absolute risk of harm to an individual woman is very small. As the authors point out, the increased risk of the estrogen/progestin combination means that in 10 000 women taking the drug for a year (10 000 must be used to register risks in whole integers), there will be 7 more coronary heart disease events, 8 more invasive breast cancers, 8 more strokes, and 8 more pulmonary emboli, but 6 fewer colorectal cancers and 5 fewer hip fractures. Nevertheless, when counting all events over the 5.2 years of the trial, the excess number of events in the active drug group was 100 per 10 000 (or 1 in 100 women). This is still a small risk, but it demonstrates that risks from the drug add up over time.

INTRODUCTION

AUTHOR/ARTICLE INFORMATION

REFERENCES

Second, the whole purpose of healthy women taking long-term estrogen/progestin therapy is to preserve health and prevent disease. The results of this study provide strong evidence that the opposite is happening for important aspects of women's health, even if the absolute risk is low. Given these results, we recommend that clinicians stop prescribing this combination for long-term use. Primum non nocere applies especially to preventive health care. The results are for a single dosing regimen (1 daily tablet containing 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate) and other regimens may have different results, but the 3 studies reported to date in the United States with other regimens have all found an increased risk of breast cancer.[5, 6, 17]

How can women be protected against osteoporosis? The results from the WHI and from numerous other studies have shown protection with hormone replacement therapy. Fortunately, there are alternative preventive strategies, at least one of which also lowers the risk of breast cancer (although to date, cardiovascular effects are not clear).[18] What about short-term use for managing menopausal symptoms? The WHI trial does not specifically address this question, but the results suggest short-term use (≤1 year) of the combination has risks for coronary heart disease and thromboembolic disease. The possibility of these small absolute risks must be balanced against the severity of symptoms and benefit of treatment.

Common preventive therapies require rigorous evaluation. For hormone replacement therapy, which is used by millions of patients, even rare adverse effects can harm substantial numbers of women. Although prevention trials are difficult and expensive (the expense often pales compared with drug expenses over time), these studies have produced important results for health care, as demonstrated by the WHI, the Breast Cancer Prevention Trial,[19] and the Multiple Outcomes of Raloxifene Evaluation study.[20] The WHI provides an

important health answer for generations of healthy postmenopausal women to come—do not use estrogen/progestin to prevent chronic disease.

INTRODUCTION

AUTHOR/ARTICLE INFORMATION

REFERENCES

Author/Article Information

Author Affiliations: Department of Ambulatory Care and Prevention (Dr Fletcher) and the Channing Laboratory, Department of Medicine (Dr Colditz), Harvard Medical School, Department of Epidemiology, Harvard School of Public Health (Drs Fletcher and Colditz), and Harvard Pilgrim Health Care (Dr Fletcher), Boston, Mass.

Corresponding Author and Reprints: Suzanne W. Fletcher, MD, MSc, Department of Ambulatory Care and Prevention, 133 Brookline Ave, Sixth Floor, Boston, MA 02215 (e-mail: Suzanne_Fletcher@hms.harvard.edu).

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INTRODUCTION

AUTHOR/ARTICLE INFORMATION

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INTRODUCTION

AUTHOR/ARTICLE INFORMATION

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INTRODUCTION

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